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Aortic Impedance in *Little* Mice

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Abstract

The *Little* dwarf mouse lives 30% longer than its age-matched wild-type (*WT*) mouse. We determined aortic input impedance in 21 (8 *Little*, 13 *WT*) 4 month-old mice. Modulus of impedance was calculated from the Fourier transformed aortic pressure (*P*) and average luminal flow velocity (V_{avg}) as $|Z_i| = |P|/|V_{avg}|$. Characteristic impedance was estimated by averaging the 2nd-10th harmonic of the impedance moduli. We found the impedance modulus $|Z_i|$ to be similar in the 2 groups (*WT* vs. *Little*; mean±SE) – peripheral resistance (10597±654 vs. 12932±1433 dyne-s/cm³), modulus at first harmonic (Z : 740±56 vs. 902±105 dyne-s/cm³ *I*), and characteristic impedance (Z : 441±34 vs. 470±60 dyne-s/cm³ *c*). Also, mean aortic velocity (20.1±1.1 vs. 16.5±1.8 cm/s) and mean aortic blood pressure (81.1±3.9 vs. 75.9±5.9 mmHg) were similar between the two groups. Impedance at low frequencies was slightly higher in the dwarf mice which may be due to the diminished systolic function as indicated by significant reduction in peak aortic velocity (84.0±3.2 vs. 70.1±1.2 cm/s, *p*<0.01). Although modestly higher, the overall impedance in *Little* mice was similar to that in *WT* mice. This indicates that left ventricular (LV) afterload may not significantly be altered in *Little* mice.

Keywords

Aortic impedance; Blood pressure; Blood flow velocity; *Little* mouse

I. INTRODUCTION

The *Little* dwarf mouse is generated due to a mutation in the hypothalamic growth hormone-releasing hormone receptor which causes deficiencies in growth hormone (GH) and insulin-like growth factor-1 (IGF-I) [1,2]. These deficiencies cause the *Little* mouse to be about 30% smaller in size but it lives about 30% longer than its wild-type littermates [3]. Despite having significant deficiencies in GH the *Little* mice have normal hematopoiesis and normal thyroid function [4]. The anabolic effects of GH/IGF-I are well recognized but little is known about the effect of their deficiency on mouse cardiovascular function. Previously, we found that resting cardiac function is depressed in *Little* mice but their response to stress is not diminished when compared to their *WT* counterparts [5]. In this study we examined the aortic input impedance in young *Little* mice under resting conditions to evaluate any differences with their *WT* littermates.

Aortic impedance is typically determined using pressure and volume flow at a given arterial location [6], but we determined impedance using pressure and flow velocity signals both of which are independent of body size [7,8]. Mouse aortic velocity signals contain a broad frequency spectrum or range of velocities. Because the Doppler sample volume covers the

entire lumen of aorta at the measurement site, the broad range of velocities (Fig. 1) suggests a nearly parabolic velocity profile (where $v_{avg} \approx \frac{1}{2}v_{peak}$). Thus we calculated impedance using $\frac{1}{2}v_{peak}$ as an estimate of average aortic luminal velocity [8].

II. METHODS

Eight *Little* and thirteen *WT* mice (4 months of age) were used in the study. Mice were anesthetized with pentobarbital sodium given intraperitoneally (4 mg/ml, 10 μ l/g body weight of mouse). The neck and xiphoid areas were shaved and the mouse was placed in a supine position with its paws taped to electrodes on an ECG board. The right carotid artery of the mouse was cannulated with a modified RADI catheter (PressureWire³, RADI Medical System, Uppsala, Sweden) and advanced into the ascending aorta. Aortic blood velocity was measured with a 10 MHz pulsed Doppler probe placed externally and oriented such that the sample volume was at the same location in the aorta as the sensor of the catheter. A 2-second long segment of blood pressure and quadrature Doppler audio signals was acquired by a Doppler signal processing workstation (Indus Instruments, Houston, Texas). Peak velocity envelope and blood pressure signals were extracted from the stored data file, and a DFT was performed on each signal to obtain magnitude and phase spectra. The modulus of input impedance was then calculated as $|Z_i| = |P|/|V_{avg}|$, where $|P|$ and $|V_{avg}|$ are the pressure and average luminal velocity moduli, respectively. Impedance values at zero and first 10 harmonics were calculated and characteristic impedance was estimated by averaging the 2nd-10th harmonic of the impedance moduli [8].

III. RESULTS

The data (mean $\pm$ SEM) are shown in Table 1. The body weight of *Little* mice was significantly lower than their *WT* littermates but both groups had similar heart rates. The noninvasively measured peak aortic flow velocity was significantly lower in the *Little* mice while mean flow velocity was on the cusp of significance. No significant differences were observed in the systolic, diastolic, mean, and pulse pressures of the two groups. Although not significant different, the overall impedance modulus (peripheral resistance - Z_o , impedance at heart period - Z_1 , and characteristic impedance - Z_c) was slightly higher in *Little* mice when compared to their *WT* littermates.

IV. DISCUSSION

Dwarf mice have increased longevity [3,9,10] and therefore are of interest in gerontology. However, many of these mice have complex lesions with multiple endocrine changes. The *Little* dwarf mouse is generated by a missense mutation in the growth hormone releasing hormone receptor [11], but the rest of its pituitary is intact and thus has normal thyroid function [9]. This mouse has reduced levels of circulating insulin-like growth factor I (IGF-I) [12] and has about 1% of normal levels of circulating growth hormone [9,10]. As a result, they weigh about a third less [3,9] and live a third longer than their *WT* littermates [3,10].

Growth hormone deficiency is associated with significant reduction in body weight in humans [13] and mice [9,14]. Miller et al. [14] reported that low body weight at young age is a significant predictor of prolonged life span in mice. In our study the young *Little* mice have significantly decreased body weight (43% lower) compared to their *WT* littermates.

Peak aortic velocity is used as a noninvasive index of cardiac output was significantly lower in *Little* mice compared to *WT* mice indicating diminished cardiac output. Although slightly lower in the *Little* mice, the pressure indices were not significantly different. As a result

impedance was slightly higher in *Little* mice suggestive of a modest increase in afterload. Increased impedance is an indicator of aortic stiffness as reflected by higher systolic blood pressure and pulse pressure in mice [8] and men [7]. But *Little* mice had similar if not lower aortic blood pressures compared to *WT* mice. This suggests that there may be other structural differences in aorta. Zaina and Pettersson [15] reported that despite 30% reduction in weight of IGF-2 deficient dwarf mice the aortic lumen diameter was of normal size while the heart and other organs were scaled accordingly. Despite the small size of *Little* mice (smallest was 12.3g) cannulation of the carotid was relatively easy suggesting near normal aortic lumen diameter in them.

The lack of significant differences in the impedance parameters - Z_0 , Z_c , despite lower velocities may have been due to highly variable pressure signals. Also, the normalized ratio of Z_c/Z_0 is not different between the groups indicating a similar afterload in the 2 groups. The values of Z_0 , Z_c , and Z_1 in *WT* mice are similar to those we previously reported [8].

In conclusion, *Little* dwarf mice have impedance similar to their *WT* littermates indicating that LV afterload may not significantly be altered in these mice. Experimental observations during surgery suggest that the aorta in the *Little* mice may not have followed scaling laws. The effect of such differences on ventricular-vascular coupling need to be further investigated.

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Table 1Data from *WT* and *Little* mice

Parameter	WT	Little	p-value
HR, bpm	394±18	360±27	NS
BW, g	24.4±0.6	14.0±0.3	<0.01
AV, cm/s	84.0±3.2	70.1±1.2	<0.01
MV, cm/s	20.1±1.1	16.5±1.8	0.053
SP, mmHg	93.5±4.2	89.3±6.0	NS
DP, mmHg	69.0±3.5	65.0±5.8	NS
MP, mmHg	81.1±3.9	75.9±5.9	NS
PP, mmHg	24.5±1.9	24.3±1.8	NS
Z ₀ , dynes-s/cm ³	10597±654	12932±1433	NS
Z ₁ , dynes-s/cm ³	740±56	902±105	NS
Z _c , dynes-s/cm ³	441±34	470±60	NS

SP-systolic, DP-diastolic, MP-mean, PP-pulse pressures; AV-peak, MV-mean aortic velocities; BW-body weight; HR-heart rate